

Kinetics & Mechanism of Base-catalysed Hydrolysis of Formamide— Effect of Alkalinity on the Reactive Tetrahedral Addition Intermediates

M. NIYAZ KHAN, RAIS AHMAD & A. AZIZ KHAN*
Department of Chemistry, Aligarh Muslim University, Aligarh

Received 16 August 1975; accepted 16 June 1976

The kinetics of base-catalysed hydrolysis of formamide have been carried out in sodium hydroxide solution (0.02-1.0M). The observed pseudo-first order rate constant is found to fit empirically in the equation $1/k_{\text{obs}} = B_1 + B_2/[\text{OH}^-]$ in lower alkaline range while it is independent of [alkali] in the higher range. The empirical parameters B_1 and B_2 have been determined using least square technique and a plausible mechanism has been suggested. The temperature dependence of hydrolysis has also been studied within the range of 56° to 85° and various activation parameters have been evaluated.

THE mechanism of acyl transfer reactions¹ has been the subject of many investigations. The existence of mono- and oxydianionic tetrahedral addition intermediates of acyl substrates²⁻⁵ has been envisaged depending upon the nature of the acyl substrate and the alkalinity of the reaction medium. In view of our earlier work⁶ on the kinetics of base-catalysed hydrolysis of succinamic and phthalamic acids and in view of the fact that no such studies have been carried out on formamide led us to undertake the present investigation. An attempt has also been made to test existence of oxydianionic addition intermediate in the hydrolysis of formamide in strongly alkaline medium.

Materials and Methods

All the chemicals used were of reagent grade. Formamide (E. Merck) was used as such. The ionic strength was adjusted by the addition of sodium nitrate. Nessler's reagent was prepared according to the method described by Vogel⁷.

The kinetic procedures used were the same as described in a previous communication⁶. All the kinetic runs were followed under pseudo-conditions and the observed pseudo-first order rate constants were evaluated using first order rate equation.

Results

The concentration dependence of hydrolysis of formamide was studied in the concentration range of 0.002 to 0.010M at 85°. The observed pseudo-first order rate constants were found to be almost insensitive to the initial [substrate].

The effect of varying temperature in the range 56-85° on the hydrolysis of formamide was also studied. The results were found to be in good agreement with Arrhenius and Eyring equations

$$k = A \exp(-E_a/RT) \quad \dots(1)$$

$$k = \frac{K_B T}{h} \exp\left(\frac{\Delta S^*}{R} - \frac{\Delta H^*}{RT}\right) \quad \dots(2)$$

where all the symbols have their usual meaning. The pre-exponential factor A and various activation parameters were evaluated using linear least square technique. The results obtained are: $\ln A$ (A in sec^{-1}) = 6.95 ± 1.18 ; E_a (kcal mole^{-1}) = 11.0 ± 0.4 ; ΔS^* ($\text{cal deg}^{-1} \text{mole}^{-1}$) = -47.1 ± 1.2 ; ΔH^* (kcal mole^{-1}) = 10.3 ± 0.4 ; ΔF_{80}^* (kcal mole^{-1}) = 26.9 . A computer programme developed in FORTRAN IV (IBM 1130) was used for these calculations.

A series of kinetic runs were carried out at different temperatures with alkali concentrations ranging from 0.02 to 1.0M. The ionic strength was kept constant at 1.5M with sodium nitrate. The observed results are shown graphically in Fig. 1. It is evident that the rate constant increases with the $[\text{OH}^-]$ in the lower range while in relatively higher range the rate becomes independent of $[\text{OH}^-]$. Similar results were recently observed in our alkaline hydrolysis of salicylamide⁸ and succinamic acid⁶. The observed pseudo-first order rate constants were

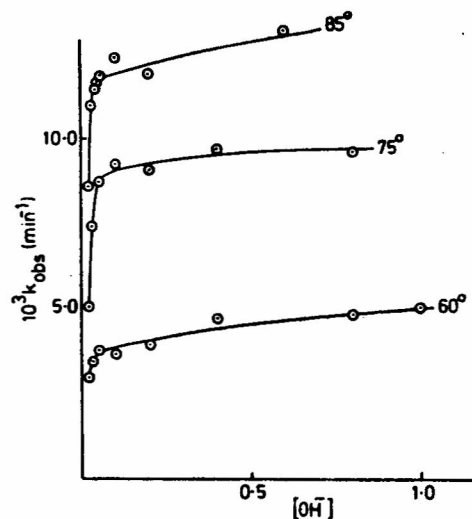


Fig. 1 — Plots showing observed pseudo-first order rate constants dependence on [hydroxide ion]

*To whom all correspondence be addressed.

found to follow the empirical equation

$$\frac{1}{k_{\text{obs}}} = B_1 + \frac{B_2}{[\text{OH}^-]} \quad \dots(3)$$

at low $[\text{OH}^-]$ (Fig. 2). The linear adjustable parameters B_1 and B_2 were evaluated using least square technique. The results at different temperatures are summarized in Table 1. The validity of Eq. (3) is evident from the root mean square deviations and maximum deviations between observed and calculated values as recorded in Table 1.

Discussion

From the earlier studies as reviewed by Jencks² it is evident that the interpretation of the mechanism of acyl transfer reactions is complicated by the fact that observed rate constants frequently include the equilibrium constants for the formation of the tetrahedral addition intermediates and are affected by resonance stabilization of the starting material to varying degrees. The direct experimental evidence for the isolation of tetrahedral intermediate in an acyl transfer reaction was observed by Rogers and Bruice⁹. A direct evidence of the accumulation of the tetrahedral addition intermediates in the hydrolysis of phthalimidium cation has been reported by Gravits and Jencks¹⁰. The recent claim¹¹ of the experimentally observed accumulation of this intermediate in the alkaline hydrolysis of anilides has been questioned by Pollack and Dumsha¹², and Guthrie¹³. The kinetic results of the present study, however, reveal the absence of such a transient reactive intermediate, the existence of which is largely controlled by resonance stabilizing capacity of the acyl substrate. This fact was recently realized in the second step hydrolysis of succinimide¹⁴, phthalimide (unpublished data), amic

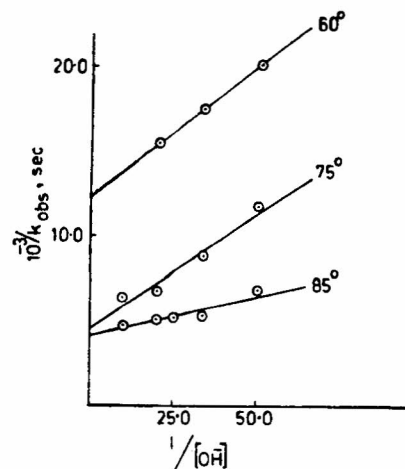
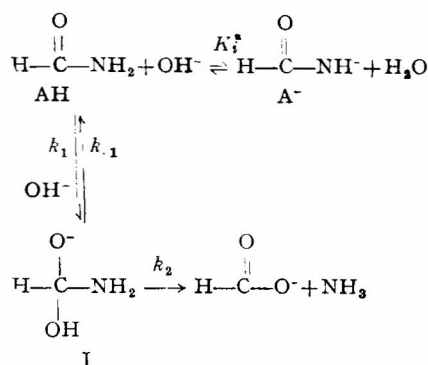


Fig. 2 — Plots of $1/k_{\text{obs}}$ versus $1/[\text{OH}^-]$ for the hydrolysis of formamide in the lower region of $[\text{OH}^-]$



Scheme 1

acids and in many other acyl transfer reactions¹⁵. Thus the mechanism to which we are led is shown in Scheme 1.

The steady state treatment to the reactive tetrahedral addition intermediate I leads to the following rate law (Eq. 4):

$$k_{\text{obs}} = \frac{k_1 k_2 [\text{OH}^-]}{\left(1 + K_i \frac{[\text{OH}^-]}{[\text{H}_2\text{O}]}\right) (k_{-1} + k_2)} \quad \dots(4)$$

where

$$\frac{K_i}{[\text{H}_2\text{O}]} = \frac{K_a}{K_w}, \text{ with } K_a = \frac{[\text{A}^-][\text{H}^+]}{[\text{AH}]} \text{ and } K_w = [\text{H}^+][\text{OH}^-]$$

Eq. (4) is reduced to Eq. (5) if $k_{-1} < k_2$ which implies that there exists a rapid equilibrium between formamide and tetrahedral intermediate

$$k_{\text{obs}} = \frac{K_I k_2 [\text{OH}^-]}{1 + \frac{K_a}{K_w} [\text{OH}^-]} \quad \dots(5)$$

where $K_I = \frac{k_1}{k_{-1}}$.

Eq. (5) is similar to the best fitted empirical Eq. (3) with

$$B_1 = \frac{K_a}{K_w K_I k_2} \text{ and } B_2 = \frac{1}{K_I k_2}$$

TABLE 1 — LINEAR PARAMETERS CORRESPONDING TO $1/k_{\text{obs}} = B_1 + B_2/[\text{OH}^-]$

| Temp. (°C) | {[Formamide] = 0.005M; μ = 1.5M} | | | | |
|------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------|-------------------|
| | $10^{-3} B_1$ sec | $10^{-1} B_2$ M sec ² | (a) K_a/K_w (mole ⁻¹) | (b) R_{ms} | (c) Max. dev. (%) |
| 60 | 12.4 | 15.8 | 78.4 | 6.50 | 0.2 |
| | ± 0.1 (d) | ± 0.2 (d) | | $\times 10^{-11}$ | |
| 60 | — | — | 11.9(e) | — | — |
| 60 | — | — | 7.2(f) | — | — |
| 75 | 4.5 | 13.5 | 33.3 | 1.87 | -10.1 |
| | ± 1.0 | ± 3.1 | | $\times 10^{-6}$ | |
| 80 | — | — | 6.9(e) | — | — |
| 85 | 4.1 | 5.2 | 78.8 | 1.30 | 6.7 |
| | ± 0.3 | ± 1.1 | | $\times 10^{-6}$ | |
| 90 | — | — | 6.6(e) | — | — |
| 90 | — | — | 13.6(f) | — | — |

(a) $K_a/K_w = B_1/B_2$.

(b) Root mean square deviation between observed and calculated values.

(c) Maximum deviation between observed and calculated values.

(d) Error limits are standard deviations.

(e, f) Values obtained in the hydrolysis of succinamic acid⁶ and in the second step hydrolysis of succinimide¹⁴ at $\mu = 1.5$.

At relatively higher concentration of hydroxide ion the condition that $1 < K_a/K_w[H^-]$ is found to be kinetically more pronounced and hence Eq. (5) is further reduced to Eq. (6) which shows that the reaction is independent of [hydroxide ion].

$$k_{\text{obs}} = \frac{K_w K_f k_2}{K_a} \quad \dots(6)$$

The ratio B_1/B_2 given in Table 1 gives the value of K_a . The results indicate that K_a is the acidity constant of an extremely weak acid and is of the order of 10^{-13} . Such an order of acidity constant has already been reported by Bruylants and Kezdy¹⁶⁻¹⁷ in the alkaline hydrolysis of substituted acetamides and by us on the hydrolysis of succinamic acid⁶ and second step hydrolysis of succinimide¹⁴. The acidity constants of amide proton of succinamic acid and formamide at different temperatures (Table 1) indicate that the values for formamide are larger than those for succinamic acid. This is acceptable because the presence of ionized carboxylic group in succinamic acid reduces its acidity of amide group.

Although Scheme 1 is sufficient to account for the observed rate data where the conjugate base A^- is taken as unreactive species^{5,11,17} yet an alternate reaction path^{1b} assuming A^- as a reactive species cannot be kinetically ruled out as it gives the same addition intermediate.

The present studies support the earlier contention that the existence of oxydianionic tetrahedral addition intermediate is not the discrete function of either the alkalinity of the reaction medium or the structural nature of the acyl substrate but it is rather completely controlled by the composite function of both the effects.

Acknowledgement

The authors thank Prof. Wasiur Rahman for facilities. M. Niyaz Khan and Rais Ahmad are obliged to the CSIR, New Delhi, for financial assistance.

References

- (a) BRUCE, T. C. & BENKOVIC, S. J., *Biorganic mechanism*, Vol. I (W. A. Benjamin, New York), 1966, 1-211; (b) JENCKS, W. P., *Catalysis in chemistry and enzymology* (McGraw-Hill, New York), 1969, 463-554; (c) BENDER, M. L., *Mechanism of homogeneous catalysis from proton to proteins* (Wiley-Interscience, New York), 1971, 72-144.
- JENCKS, W. P., *Chem. Rev.*, **72** (1972), 705.
- FEDOR, L. R. & BRUCE, T. C., *J. Am. chem. Soc.*, **87** (1965), 4138.
- BENDER, M. L. & HECK, H. d-A., *J. Am. chem. Soc.*, **89** (1967), 1211.
- BIECHLER, S. S. & TAFT (Jr), R. W., *J. Am. chem. Soc.*, **79** (1957), 4927.
- KHAN, M. N. & KHAN, A. A., *Indian J. Chem.*, **13** (1975), 485.
- VOGEL, A. I., *A text book of quantitative inorganic analysis* (Longmans Green, London), 1955, 643.
- AHMAD, R., KHAN, M. N. & KHAN, A. A., *Indian J. Chem.*, (for publication).
- ROGERS, G. A. & BRUCE, T. C., *J. Am. chem. Soc.*, **95** (1973), 4452.
- GRAVITZ, N. & JENCKS, W. P., *J. Am. chem. Soc.*, **96** (1974), 489.
- STAUFFER, C. E., *J. Am. chem. Soc.*, **96** (1974), 2489.
- POLLACK, R. M. & DUMSHA, T. C., *J. Am. chem. Soc.*, **97** (1975), 377.
- GUTHRIE, J. P., *J. Am. chem. Soc.*, **95** (1973), 6999; **96** (1974), 588.
- KHAN, M. N. & KHAN, A. A., *J. org. Chem.*, **40** (1975), 1793.
- GRAVITZ, N. & JENCKS, W. P., *J. Am. chem. Soc.*, **96** (1974), 507.
- BRUYLANTS, A. & KEZDY, F., *Rec. chem. Progr.*, **21** (1960), 213.
- KEZDY, F. & BRUYLANTS, A., *Bull. Soc. chem. Belg.*, **69** (1960), 602.